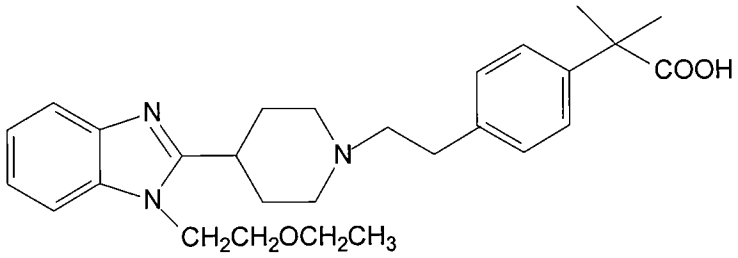
AMENDMENT(S) TO THE SPECIFICATION

Please replace the paragraph beginning at page 1, line 6, with the following rewritten paragraph:

The invention refers to a new ~~polymorphous~~ crystalline form of 4-[2-[4-[1-(2-ethoxyethyl)-1H-benzimidazole-2-yl]-1-piperidinyl]ethyl]-αα-dimethyl-benzene~~e~~acetic acid (herein referred to as "bilastine") of formula (I).



(I)

Please replace the paragraph beginning at page 1, line 10, with the following rewritten paragraph:

From hereon referred to as ~~polymorph~~ crystalline form 1, to procedures used to prepare it, to pharmaceutical formulae that contain ~~polymorph~~ crystalline form 1 and to the use of ~~polymorph~~ crystalline form 1 to treat allergic reactions and pathological processes mediated by histamine in mammals, such as man.

Please replace the paragraph beginning at page 2, line 12, with the following rewritten paragraph:

The invention refers to ~~a pure~~ crystalline form ~~of polymorph~~ 1 of bilastine, characterised by X-ray crystallographic analysis, with approximate crystal parameters as follows:

Crystallographic system	Monoclinic~~al~~
Spatial group	P2 (1)/c
Crystal size	0.56 x 0.45 x 0.24 mm
Cell dimension	a=23.38 (5) A angstrom $\alpha = 90°$
	b=8.829 (17) A $\beta = 90°$
	c=12.59 (2) A $\gamma = 90°$
Volume	2600 A^3
Z, calculated density	4, 1.184 mg/m^3

Please replace the paragraph beginning at page 2, line 25, with the following rewritten paragraph:

The crystalline ~~polymorph~~ form 1 of bilastine is also characterised by its infrared absorption spectrum in potassium bromide tablet that has the following characteristic absorption bands, expressed in reciprocal centimeters;

3430 (s)*; 3057 (w)*; 2970 (s); 2929 (s); 2883 (m)*; 2857 (m); 2797 (w); 1667 (m); 1614 (m); 1567 (w); 1509 (s); 1481 (m); 1459 (vs)*; 1431 (m); 1378 (w); 1346 (m); 1326 (m); 1288 (w); 1254 (m); 1199 (w); 1157 (w); 1121 (vs); 1045 (w); 1020 (w); 1010 (w); 991 (w); 973 (w); 945 (w); 829 (w); 742 (s); 723 (w); 630 (w), * where (w) = weak intensity, (m) = medium intensity, (s) = strong intensity, (vs) = very strong intensity. Figure 1 represents the infrared spectrum of the crystalline ~~polymorph~~ form 1 of the bilastine in a potassium bromide tablet recorded in a Perkin Elmer Spectrum One FTIR spectrophotometer.

Please replace the brief description of the figures beginning at page 3, line 13, with the following rewritten paragraphs:

Figure 1 shows a typical infrared absorption spectrum in potassium bromide of ~~polymorph~~ crystalline form 1. (Vertical axis: Transmission (%); Horizontal axis: Wavenumber (cm^{-1})).

Figure 2 shows a typical infrared absorption spectrum in potassium bromide of ~~polymorph~~ crystalline form 2. (Vertical axis: Transmission (%); Horizontal axis: Wavenumber (cm^{-1})).

Figure 3 shows a typical infrared absorption spectrum in potassium bromide of ~~polymorph~~ crystalline form 3. (Vertical axis: Transmission (%); Horizontal axis: Wavenumber (cm^{-1})).

Please replace the paragraph beginning on page 3, at line 27, with the following rewritten paragraph:

We have found that bilastine can exist in three clearly different polymorphic forms called ~~polymorph~~ crystalline form 1, ~~polymorph~~ crystalline form 2 and ~~polymorph~~ crystalline form 3.

Please replace the paragraph beginning at page 4, at line 1, with the following rewritten paragraph:

The procedure described in US patent no. 5,877,187 generates a mixture of ~~polymorphs~~ crystalline forms 2 and 3. We have discovered experimental conditions and specific solvents to produce clearly different polymeric forms of bilastine. The crystalline ~~polymorph~~ form 1 of pure bilastine is prepared according to the procedures of this invention. The ~~polymorphic~~ crystalline forms 1 and 2 are stable. ~~Polymorph~~ Crystalline form 3 is not very stable and is difficult to obtain in the pure form. Both ~~polymorph~~ crystalline form 2 and ~~polymorph~~ crystalline form 3 are converted into ~~polymorph~~ crystalline form 1 by the procedures of this invention.

Please replace the paragraph beginning at page 4, line 10, with the following rewritten paragraph:

~~Polymorph~~ Crystalline form 1 of bilastine has a melting point of 200.3°C. ~~Polymorph~~ Crystalline form 2 has a melting point of 205.2°C. ~~Polymorph~~ Crystalline form 3 has a melting point of 197.0°C.

Please replace the paragraph beginning at page 4, line 13, with the following rewritten paragraph:

The crystalline ~~polymorphic~~ form 1 of bilastine is also characterised by its infrared absorption spectrum in potassium bromide that has the following characteristic absorption bands, expressed in reciprocal centimetres:

3430 (s)*; 3057 (w)*; 2970 (s); 2929 (s); 2883 (m)*; 2857 (m); 2797 (w); 1667 (m); 1614 (m); 1567 (w); 1509 (s); 1481 (m); 1459 (vs)*; 1431 (m); 1378 (w); 1346 (m); 1326 (m); 1288 (w); 1254 (m); 1199 (w); 1157 (w): 1121 (vs); 1045 (w); 1020 (w); 1010 (w); 991 (w); 973 (w); 945 (w); 829 (w); 742 (s); 723 (w); 630 (w), * where (w) = weak intensity, (m) = medium intensity, (s) = strong intensity, (vs) = very strong intensity. Figure 1 represents the infrared spectrum of the crystalline ~~polymorph~~ form 1 of the bilastine in a potassium bromide tablet recorded in a Perkin Elmer Spectrum One FTIR spectrophotometer.

Please replace the paragraph beginning at page 4, line 27, with the following rewritten paragraph:

The crystalline ~~polymorphic~~ form 2 of bilastine is also characterised by its infrared absorption spectrum in potassium that has the following characteristic absorption bands, expressed in reciprocal centimetres:

3429 (s)*; 3053 (w)*; 2970 (s)*; 2932 (s); 2868 (s); 2804 (w); 1699 (m); 1614 (m)*; 1567 (m); 1508 (s); 1461 (vs)*; 1381 (m); 1351 (s); 1331 (m); 1255 (m); 1201 (w); 1156 (m); 1121 (vs); 1048 (w); 995 (w); 823 (w); 767 (w); 744 (s); 724 (~~d~~ w); 630 (w), * where (w) = weak intensity, (m) = medium intensity, (s) = strong intensity, (vs) = very strong intensity. Figure 2 represents the infrared spectrum of the crystalline ~~polymorph~~ form 2 of the bilastine in a potassium bromide tablet recorded in a Perkin Elmer Spectrum One FTIR spectrophotometer.

Please replace the paragraph beginning at page 5, line 11, with the following rewritten paragraph:

The crystalline ~~polymorphic~~ form 3 of bilastine is also characterised by its infrared absorption spectrum in potassium bromide that has the following characteristic absorption bands, expressed in reciprocal centimeters:

3430 (s)*; 3053 (w)*; 2970 (s); 2932 (s); 2868 (s); 2804 (w); 1291 (w); 1708 (m)*; 1614 (m); 1568 (m); 1508 (s); 1461 (vs)*; 1380 (m); 1351 (m); 1330 (m); 1271 (m); 1255 (M); 1201 (w); 1156 (m); 1121 (vs); 1048 (w); 995 (w); 823 (M); 767 (w); 744 (s); 724 (w); 630 (w), * where (w) = weak intensity, (m) = medium intensity, (s) = strong intensity, (vs) = very strong intensity. Figure 3 represents the infrared spectrum of the crystalline ~~polymorph~~ form 3 of the bilastine in a potassium bromide tablet recorded in a Perkin Elmer Spectrum One FTIR spectrophotometer.

Please replace the paragraph beginning at page 5, line 24, with the following rewritten paragraph:

We have discovered that, under selected experimental conditions, the mixture of the ~~polymorphic~~ crystalline forms 2 and 3, obtained according to US patent no. 5,877,187, is surprisingly transformed into ~~polymorph~~ crystalline form 1. We have also discovered that ~~polymorph~~ crystalline form 1 of bilastine is very stable and is not transformed into any of the other polymorphs 2 and 3. Similarly, in the same experimental conditions, the pure ~~polymorphic~~ crystalline form 2 of bilastine is surprisingly transformed into the pure ~~polymorphic~~ crystalline form 1. ~~Polymorphic~~ Crystalline form 3, which is the most unstable, undergoes the same transformation under the same conditions.

Please replace the paragraph beginning at page 6, line 4, with the following rewritten paragraph:

~~Polymorph~~ Crystalline form 1 of bilastine is a very stable polymorph at room temperature and is, therefore, very useful as an active ingredient of a pharmaceutical preparation. ~~Polymorph~~ Crystalline form 1 is also stable when stored at temperatures above room temperature.

Please replace the paragraph beginning at page 6, line 9, with the following rewritten paragraph:

The ~~polymeric~~ crystalline form 1 of bilastine is characterised by the following data of its X-ray crystallographic analysis as a monocrystal, with crystal parameters of approximately the following values:

Crystallographic system	Monoclinic~~al~~
Spatial group	P2 (1)/c
Crystal size	0.56 x 0.45 x 0.24 mm
Cell dimension	a=23.38 (5) A angstrom $\alpha = 90°$
	b=8.829 (17) A $\beta = 90°$
	c=12.59 (2) A $\gamma = 90°$
Volume	2600 A^3
Z, calculated density	4, 1.184 mg/m^3

Please replace the paragraph beginning at page 6, line 22, with the following rewritten paragraph:

During the development of ~~polymorph~~ crystalline form 1 of bilastine for pharmaceutical preparations, elaborated according to correct manufacturing procedures, we have discovered that crystallization of bilastine (prepared according to the description given in US patent no 5,877,187) from ~~short chained alcohols, preferably~~ isopropylic alcohol and n-butanol ~~and mixtures thereof~~, leads to generation of the ~~pure~~ polymeric form 1 of bilastine with a high yield. Crystallization ~~of~~ from acetone, ~~dimethylsulphoxide~~, dimethylsulfoxide, dimethylformamide, acetonitrile, and tetrahydrofurane or its mixtures thereof also lead to generation of ~~polymorph~~ crystalline form 1, although with lower yields. It is, therefore, preferable to use the former solvents.

Please replace the paragraph beginning on page 7, line 4, with the following rewritten paragraph:

The infrared spectrum of ~~polymorph~~ crystalline form 1of bilastine in potassium bromide is characterised by the following bands, absent from polymorphs 2 and 3:

Wavenumber (cm^{-1})

3057

2929

2883

2857

2797

1667

1481

1431

1346

1326

1288

973

945

829

Please replace the paragraph beginning on page 7, line 23, with the following rewritten paragraph:

Figure 1 shows the complete infrared spectrum of ~~polymorph~~ crystalline form 1 of bilastine in potassium bromide, recorded with a Perkin Elmer Spectrum One ~~transformer~~ spectrophotometer.

Please replace the paragraph beginning on page 8, line 1, with the following rewritten paragraph:

Pharmaceutical preparations of this invention can contain, as well as an effective quantity of ~~polymorph~~ crystalline form 1 of bilastine as an active ingredient as an antiallergic or antihistaminic agent, several pharmaceutically acceptable excipients ~~that can be solid or liquid~~. The making of those pharmaceutical preparations implies procedures in which the active ingredient is not in any case dissolved in a solvent, thus maintaining its crystalline structure. The solid pharmaceutical preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid excipient can be one of several substances that act as diluents, aromatising agents, agglutinants or disintegrating agents and an encapsulation material. The powders and tablets preferentially contain from approximately 5 to approximately 20 per cent of the active ingredient. Appropriate solid excipients are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, waxes with low melting point, cocoa butter and similar products. The term "preparations" includes the formulation of the active ingredient with an excipient for

encapsulation to produce a capsule in which the active ingredient (with or without other excipients) is surrounded with the excipient by an encapsulation material. Tablets, powders, ~~stamps~~ cachets and capsules can be used as suitable forms for oral administration. The active ingredient can also be incorporated into a chewing gum that can contain sweeteners, flavorings and colorings as appropriate.

Please replace the paragraph beginning at page 8, line 28, with the following rewritten paragraph:

Liquid preparations ~~include~~ comprise suspensions, ~~solutions and emulsions. An example of these corresponds to aqueous suspensions~~ that can be made by mixing the finely divided active ingredient in water with suspension agents. ~~Aqueous solutions can be prepared by placing the active ingredient in water and adding suitable coloring agents, aromas, stabilising agents, sweeteners, solubilising and thickening agents as appropriate.~~

Please replace the paragraph beginning at page 9, line 6, with the following rewritten paragraph:

Also, topical preparations are considered for nasal, ophthalmic and dermal use. Appropriate formulae for nasal administration can correspond to solutions or suspensions. Ophthalmic formulae can be ~~solutions,~~ suspensions ~~or~~ and ointments. Dermal preparations can be ~~solutions,~~ suspensions, ointments and creams. Ointments usually contain lipophylic excipients such as mineral oil or vaseline. ~~Solutions for ophthalmic use can contain sodium chloride, acid and/or base to adjust the pH, and purified water and preservatives.~~

Please replace the paragraph beginning at page 9, line 20, with the following rewritten paragraph:

The effective antiallergic or antihistaminic amount of ~~polymorph~~ crystalline form 1 of bilastine for topical administration varies between 0.1 and 5% of the total weight of the pharmaceutical compound. The preferred amount ranges from 0.1 to 2% of the total weight of the pharmaceutical compound.

Please replace the paragraph beginning at page 9, line 25, with the following rewritten paragraph:

The effective antiallergic or antihistaminic amount of ~~polymorph~~ crystalline form 1 of bilastine for oral administration varies from 1 to 50 mg/day, with preferably an amount corresponding to approximately 2 to 20 mg/day in a single or fractionated doses.

Please replace the paragraph beginning at page 10, line 1, with the following rewritten paragraph:

~~Polymorph~~ Crystalline form 1 of bilastine has antihistaminic properties that have been demonstrated in experimental pharmacological models, such as preventing histamine-induced lethality in guinea-pig and antagonism against cutaneous capillary permeability induced by histamine in the rat.

Please replace the paragraph beginning at page 10, line 9, with the following rewritten paragraph:

EXAMPLE 1

Preparation of ~~polymorph~~ crystalline form 1 of bilastine

Dissolve bilastine (see the US patent no. 5~~3~~,877,187 in isopropylic alcohol heated to reflux for approximately 15-20 minutes under nitrogen while stirring. Cool the solution to 50°C over 6 hours and stop stirring. Let the solution cool to room temperature and stir again for three hours, filter and wash with cold isopropylic alcohol. Dry the solid residue in a vacuum oven at 35-40°C to constant weight.

Please replace the paragraph beginning at page 10, line 18, with the following rewritten paragraph:

EXAMPLE 2

Preparation of ~~polymorph~~ crystalline form 1 of bilastine

Heat a suspension of bilastine (see US patent no. 5,877,187) in n-butanol and reflux for 3 hours under nitrogen while stirring . Leave the solution to cool while stirring, filter off the solid residue and dry it in a vacuum oven at 35-40°C at constant weight.

Please replace the paragraph beginning at page 10, line 25, with the following rewritten paragraph:

EXAMPLE 3

Preparation of ~~polymorph~~ crystalline form 1 of bilastine

Treat a mixture of polymorphs 2 and 3 of bilastine for several hours with hot acetone. Let the mixture cool to room temperature and filter off the solid residue. Dry it to constant weight.

Please replace the paragraph beginning at page 11, line 1, with the following rewritten paragraph:

EXAMPLE 4

Preparation of ~~polymorph~~ crystalline form 1 of bilastine

Dissolve ~~polymorph~~ crystalline form 3 of bilastine in isopropylic alcohol heated to reflux and stir for approximately 15-20 minutes under nitrogen. Let the solution reach room temperature constantly stirring, filtering and washing with cold isopropanol. Dry the solid in a vacuum oven at 35-40°C to constant weight.

Please replace the paragraph beginning on page 11, line 10, with the following rewritten paragraph:

EXAMPLE 5

Preparation of ~~polymorph~~ crystalline form 1 of bilastine

Dissolve ~~polymorph~~ crystalline form 2 of bilastine in n-butanol heated to reflux while stirring for approximately 3 hours. Let the solution reach room temperature while stirring, filtering and draining. Dry the solid in a vacuum oven at 35-40°C to constant weight.

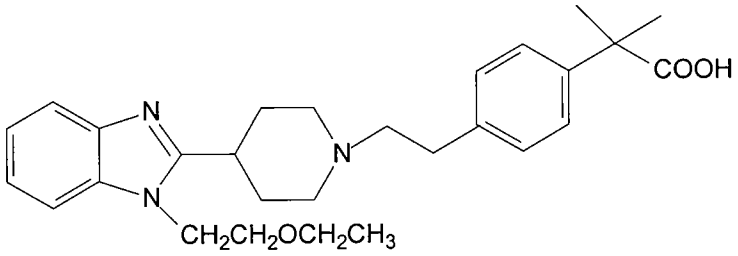
In the Abstract:

Please amend the Abstract as follows –

ABSTRACT

~~Polymorph~~ Crystalline form 1 of 4-[2-[4-[1-(2-ethoxyethyl)-1H-benzimidazole-2-yl]-1-piperidinyl]ethyl]-αα-dimethyl-benzeneacetic acid

~~Polymorph~~ Crystalline form 1 of 4-[2-[4-[1-(2-ethoxyethyl)-1H-benzimidazole-2-yl]-1-piperidinyl]ethyl]-αα-dimethyl-benzeneeacetic acid of formula (I) is described, procedures for its preparation, pharmaceutical formulae containing ~~polymorph~~ crystalline form 1 and the use of ~~polymorph~~ crystalline form 1 to treat allergic reactions and pathological processes mediated by histamine in mammals such as man.



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